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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/244,195	02/04/1999	GEORGE BARRIE KITTO	D6073	3475

32425 7590 01/26/2005

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/244,195	KITTO ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the submission filed 01 November, 2004, wherein claim 6 was amended.[1] Claims 6, 8-10, 12, and 13 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

Claims 6, 8-10, 12, and 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Claim 6 recites the limitation "said transactivating protein". There is insufficient antecedent basis for this limitation in the claim.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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[1] Applicants are advised that the amendment filed 01 November, 2004, failed to include the status of claim 8 as required pursuant to 37 C.F.R. 1.121(c). However, since the claim was included in the arguments section of applicants' response, the examiner will assume that it is still pending.

> Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 6, 8-10, 12, and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994) and Thimmig *et al.* (1993). As previously set forth, Brey *et al.* (1992) describe the preparation of S. *typhimurium* expression systems (including those derived from strain SL3261) that are useful for the expression of heterologous (e.g., malaria) antigens. A detailed description of suitable expression vectors can be found in Table 1 and column 20. This publications also discloses that said expression systems are particularly useful because the vectors of interest retain their enteroinvasive properties but are markedly reduced in terms of virulence. This properties make these vectors particularly useful for generating both humoral and cell-mediated immune responses against the antigen

of interest (see col. 7, first paragraph). Various vaccine formulations can be prepared and routes of administration utilized (i.e., oral, intradermal, intramuscular, intraperitoneal, intranasal, etc.) (see col. 21, section 5.6). A particularly attractive feature of this vector system is the ability of S. *typhimurium* to invade the gut epithelial tissue thereby leading to strong mucosal and helper immune responses (see cols. 23 and 24, section 5.6.2). Other advantages of this vector system include the lack of a necessary purification step for the immunogen of interest and the ability of this system to be inexpensively produced and conveniently administered. The probability of adverse reactions in both animals and humans is also low. This teaching does not disclose the utilization of an Lpp-OmpA-RT fusion protein.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *reverse transcriptase* gene.

Thimmig and colleague provide the complete nucleotide/amino acid sequence of the HIV-1 RT gene and expression vectors comprising

said gene. For instance, see MATERIALS AND METHODS, p. 16529, and Results, pages 16530-16533, wherein the gene, expression vectors, and cell lines producing said protein are described. Thus, this teaching clearly illustrates that HIV-1 RT was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 RT gene provided by Thimmig *et al.* (1993), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 RT-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 RT since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Response to Arguments

Applicants traverse and submit that the prior art fails to teach or suggest fusion constructs employing RT. This argument is clearly not persuasive. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that

a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). In this case, the prior art clearly provides efficient tools for making large quantities of heterologous proteins that retain the natural conformations and biochemical activities. The only issue is whether one of ordinary skill in the art would have been motivated to prepare RT fusion constructs using these reagents. The answer to this question is emphatically yes. The human immunodeficiency virus type 1 is the aetiological agent of AIDS. One of ordinary skill in the art would have had more than sufficient motivation to prepare RT fusion constructs because of the medical importance of this virus and gene product. Utilizing the Salmonella expression system would provide a facile means for generating large quantities of an immunogenic protein that will be capable of inducing both humoral and cell-mediated immune response.

Claims 6, 8-10, 12, and 13[2] are rejected under 35 U.S.C. § 103(a) as being obvious over Hone *et al.* (1996) in view of Georgiou *et al.*

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[2] As previously set forth, the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

(1994) and Thimmig *et al.* (1993). Hone and colleagues provide attenuated *Salmonella typhimurium* vaccine vectors containing expression vectors encoding *Escherichia coli* OmpA::HIV-1 gp120 fusion proteins. These Salmonella strains induced both mucosal and systemic HIV-1 gp120-specific immune responses. The authors concluded (see Abstract, p. 203) that "These results, therefore, support the proposal that *Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments." The authors also noted (p. 206, penultimate paragraph) that "It is reasonable to propose, therefore, that *Salmonella* bearing surface-expressed rgp120 will elicit gp120-specific $CD8^+$ CTLs." This teaching does not disclose Lpp-OmpA-HIV-1 Tat fusion proteins.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see cols. 3, 4, 15, and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium. It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene.

Thimmig and colleague provide the complete nucleotide/amino acid

sequence of the HIV-1 RT gene and expression vectors comprising said gene. For instance, see MATERIALS AND METHODS, p. 16529, and Results, pages 16530-16533, wherein the gene, expression vectors, and cell lines producing said protein are described. Thus, this teaching clearly illustrates that HIV-1 RT was widely available and of obvious diagnostic and medical importance.

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U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). In this case, the prior art clearly provides efficient tools for making large quantities of heterologous proteins that retain the natural conformations and biochemical activities. The only issue is whether one of ordinary skill in the art would have been motivated to prepare RT fusion constructs using these reagents. The answer to this question is emphatically yes. The human immunodeficiency virus type 1 is the aetiological agent of AIDS. One of ordinary skill in the art would have had more than sufficient motivation to prepare RT fusion constructs because of the medical importance of this virus and gene product. Utilizing the Salmonella expression system would provide a facile means for generating large quantities of an immunogenic protein that will be capable of inducing both humoral and cell-mediated immune response.

Finality of Office Action

Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE**

THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

22 January, 2005